REMARKS

The Claims:

Claims 60-68 and 73-81 are pending and under active consideration. Claims 1-59 and 69-71 are cancelled. Claims 72 and 73 are currently amended and claim 82 is newly added. Support for the amendment is found throughout the application, in particular the original claims as filed, as well as Table I in the specification.

Applicants reserve the right to filed continuing applications directed to the subject matter in the original claims as filed. Entry of the claim amendments is respectfully requested.

The Office Action:

Claim 25 is objected to for the presence informalities.

Claims 1-7, 9-57, 59-66, 68, 73-79 and 81 are rejected under 35 USC § 112, first paragraph.

Claims 1-7, 9-57, 59-66, and 68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 7,064,211 to Kowalczyk et al.

Objection to the Claims

Claim 25 is objected to for the presence informalities. In view of the amendment canceling claim 25, this objection is rendered moot.

Rejection under 35 USC § 112

Claims 1-7, 9-57, 59-66, 68, 73-79 and 81 are rejected under 35 USC § 112, first paragraph. According to the Office Action, "the specification, while being enabling for certain compounds of formula II such as example 57 and 129 in the treatment of certain cancers such as breast, colon, melanoma, etc., does not reasonably provide enablement for all compounds of formula II in the treatment of every single cancer."

As amended, the present claims are directed to uses with only compounds of Example 57 and 129, which the Office Action has acknowledged are enabled for the treatment of certain cancers. Accordingly, this rejection is rendered partially moot.

Applicants respectfully disagree with the Office Action's contention that the claims are not enabled because the specification does not describe the treatment "of every single cancer". The claims are limited to tumors resistant to at least one chemotherapeutic agent and thus do not pertain to *all* cancers.

Moreover, according to § 2164.03 of the MPEP, even in unpredictable arts, a disclosure of every operable species is not required. *Citing In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). Representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. MPEP § 2164.02.

Applicants have demonstrated the ability of the claimed compounds to inhibit cell growth in a myriad of tumor cell lines. In particular, Example 129 is a potent inhibitor of cell growth in 34 tumor cell lines and the compound's activity is independent of tumor origin. At page 107; *see also* Table 1. As illustrated in the affidavit submitted on April 11, 2008, Example 57 is also a potent inhibitor of a number of different tumor cell lines, with comparable efficacy to Example 129.

Accordingly, Applicants have provided overwheliming evidence showing enablement of the presently claimed method.

Nonetheless, the Office Action asserts that the "specification provides no direction or guidance for the treatment of mouth, pancreatic or kidney tumors… yet applicant claims the treatment of such cancers. No reasonably specific guidance is provided concerning treatment of every single cancer with the aforementioned compounds, other than melanoma, colon, breast, and epidermoid tumors… The instant disclosure provides no evidence to suggest that this unique activity can be extrapolated to brain cancer, for example, having unrelated mechanisms of resistance…" At Page 7.

Proof of enablement should be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. MPEP § 2164.02 (Emphasis Aded). Applicants have shown cellular inhibition data for a variety of different tumor cell lines, albeit not *every* tumor. The mere recitation of tumors that are not specifically disclosed/tested does not meet the burden of persuasion required under 35 U.S.C. § 112 for establishing nonenablement of a genus. *Citing Fiers v. Revel,* 984 F2.d 1164 "any party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with 35 U.S.C. § 112 bears the burden of persuasion in showing said lack of compliance."

Notwithstanding, Applicants have described a number of mechanisms by which the instant compounds obtain their broad anti-tumor activity, which does provide a reasonable basis to suggest that activity can be extrapolated to other tumors. In particular, Applicants draw the Examiners attention to pages 103-138 of the specification and the affidavit submitted on April 11, 2008. While Applicants will not recount all of the experiments and data provided therein, some of the factors that likely contribute to the presently claimed activity include: sensitivity against cells overexpressing drug efflux pumps (at page 109), inhibition of polymerization of MAP-associated tubulin in a cell-free spectrophotometric assay and depolymerization of cellular microtubules as assessed by immunofluorescence microscopy, inhibition of proliferation in 34 tumor cell lines (mean IC_{50} = 2.1 ± 1.7 nM; range 0.2 – 7 nM)

wherein cytotoxicity is independent of tumor origin, retention of sensitivity to cell lines inherently-resistant to paclitaxel (HCT15, DLD1, MX1W), induction of mitotic arrest (3 – 10 nM at 24 hr) followed by apoptosis (48 hr), and retention of potency in tumor cell lines transfected with or selected for over-expression of the drug transporters MDR1 (P-glycoprotein), MRP1, or MXR. Specification at pages 137-138.

Additionally, claims 63, 72, 76 and 82 list specific tumors and thus do not pertain to *all* tumors as rejected in the present Office Action. Notably, the tumors listed in 72 and 82 are those provided in Table I, in which cell growth was inhibited.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the enablement rejection under 35 USC § 112, first paragraph.

Rejection Under 35 USC § 103

Claims 1-7, 9-57, 59-66, and 68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 7,064,211 to Kowalczyk et al. Applicants respectfully traverse this rejection.

The Office Action identifies three Kowalczjk et al. compounds: ER-805590, ER-805711 and ER-806147, as falling within formula II, and asserts that they render obvious both the compounds in formula II, and Applicants' claimed methods. Applicants respectfully disagree.

First, Applicants respectfully assert that there is nothing in Kowalczyk et al. that would lead the art skilled to select any of these three compounds as a starting point for optimization, (i.e., as a "lead compound") as is required under Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd. (Fed. Cir. 2007). Indeed, Kowalczyk et al. provides no specific activity associated these compounds - but rather just a general statement that its compounds (such as the more than 600 compounds falling within formula I) can be used for a variety of purposes, including treating cancer, and that "certain exemplary embodiments" have IC_{50} values of less than or equal to 10 μM, while others are in the range of 0.1 nM - 10 nM. See Kowalczyk et al. at column 102. Thus, rather than identify the "predictable solutions" required for prima facie obviousness by the Supreme Court in KSR v. International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), the Office Action has employed hindsight to select these three

compounds from the broad selection of compounds and treatment methods disclosed in Kowalczjk et al.

Moreover, the claims as amended recite methods using two specific compounds – those of examples 129 and/or 57. There is nothing in the art that would have suggested making the specific molecular modifications necessary to achieve these compounds. And there is no suggestion anywhere in the art that these compounds would be effective in the treatment, inhibition or eradication of drug resistant tumors.

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. *KSR* at page 6. On the other hand, where an art is unpredictable, as the chemical arts often are, *KSR's* focus on these "identified, predictable solutions" presents a difficult hurdle because potential solutions are less likely to be genuinely predictable. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

The unpredictability in the art, the myriad of compounds and diseases to choose from, and the failure of the prior art to provide any indication why a compound having the structure of example 129 and/or 57 would be effective in the treatment, inhibition or eradication of drug resistant tumors, provides overwhelming support for the nonobviousness of the present claims. The fact that the presently claimed compounds are in fact effective in the inhibition of drug resistant tumor cell lines is a totally unexpected result that serves to further bolster the nonobviousness of the present claims. Accordingly, Applicants respectfully submit that Kowalczyk et al. fails to render the present claims obvious and request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants would like to thank the Examiner for her thorough review of the application. In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance. The Examiner is encouraged to call Applicants' representative at (973) 660-6615 if it is believed that a telephone conference would expedite the prosecution of the subject application.

Respectfully submitted,

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/Joel Silver/

Joel Silver
Reg. No. 53,866

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (973) 660-6615
Fax No. (973) 660-7973